

**Amendments to the Specification:**

Please replace the section beginning at page 1, line 1, with the following redlined section:

This application is a continuation of U.S. Patent Application No. 10/455,935, filed June 06, 2003, now abandoned; which application is a continuation of U.S. Patent Application No. 09/632,387, filed August 03, 2000, and abandoned; which application is a continuation of U.S. Patent Application No. 09/291,823, filed April 14, 1999, which issued as U.S. Patent No. 6,171,577; which application is a continuation application of U.S. Patent Application 08/690,184, filed July 26, 1996, which issued as U.S. Patent No. 5,968,477; which application is a continuation-in-part of U.S. Patent Application No. 08/351,653, filed December 07, 1994, and abandoned; which application is a continuation-in-part of U.S. Patent Application No. 08/261,064, filed June 16, 1994, and abandoned; which application is a continuation-in-part of U.S. Patent Application No. 08/185,660, filed January 24, 1994, and abandoned.

Please replace the paragraph beginning at page 29, line 1, with the following redlined paragraph:

--A preferred modified annexin molecule, as defined herein, is a monomeric form of annexin V with an N-terminal extension of an amino acid sequence, wherein the sequence is selected so that it contains amino acids adjacent to an amino acid countacy an accesible sulfhydryl group cysteine. The selected sequence will improve target to normal organ ratios and superior clot imaging potential. The use of hydrophilic amino acids, in the sequence such as serine, glycine, theonine, aspartate, glutamate and others facilitates renal excretion of chelate products of catabolism following uptake of the radiolabeled annexin in normal organs, such as the liver. One preferred amino acid sequence added to at the N-terminus of annexin V is Ala-Cys-Asp-His-Ser-Met (SEQ ID NO:1). An advantage of this particular configuration is that with the cysteine near the N-terminus, the sulfhydryl and neighboring amide groups provide for stable chelation of the technetium resulting in an N<sub>3</sub>S-like stable chelate, as in endogenous radiolabeling of the annexin molecule.--

Please replace the paragraph beginning at page 52, line 3, with the following redlined paragraph:

-- In one embodiment of the invention, a recombinant annexin molecule is modified at the N-terminus by the addition of amino acid residues, provided that at least one of the amino acids provides an accessible sulfhydryl group. For example, this can be accomplished with the addition of at least a single cysteine residue near the N-terminus. A preferred modified annexin as defined herein is a monomeric form of annexin V with an N-terminal extension of the preferred amino acid sequence of Ala-Cys-Asp-His-Ser-Met (SEQ ID NO:1). One advantage of this configuration is that with the cysteine near the N-terminus, the sulfhydryl and neighboring amide groups provide for chelation of the technetium resulting in an N<sub>3</sub>S-like stable chelating compound, for direct labeling. It is intended within the present invention that adjacent amino acid donor atoms from amino acid moieties will wrap around the base of the metal oxo bond in a square pyramidal arrangement, thus achieving stability, similar to stable chelation achieved by utilizing an N<sub>3</sub>S chelating compound.--

Please replace the paragraph beginning at page 98, line 18, with the following redlined paragraph:

--A parent clone, HPAP1.6, is described in Funakoshi et al., "Primary Structure of Human Placental Anticoagulant Protein", *Biochemistry*, Vol. 26, pp. 8087-8092 (1987). Polymerase chain reaction (PCR) was used to amplify the annexin gene from the λHPAP1.6 parent clone. The sense primer (CAT ATG GCA CAG CTT CTC A) (SEQ ID NO:2) contained an NdeI restriction site (underlined) and the first 16 nucleotides of the annexin leader sequence, beginning with the ATG start codon. The antisense primer (GGA TCC TTA GTC ATC TTC TCC ACA) (SEQ ID NO:3) encoded the end of the coding sequence, a stop codon (bold) and BamHI restriction site (underlined). The PCR product and plasmid pET-12a (Figure 2) obtained from Novagen (Palo Alto, California) were each digested with NdeI and BamHI and ligated

together with T4 DNA ligase. A portion of the ligation solution was transformed into an *E. Coli* host strain and selected on nutrient agar plates containing ampicillin. Plasmid from the resultant clone was designated pET-12a-PAP1-E287G, 7/16/93, clone 1. Dideoxy DNA sequence analysis showed that this plasmid contained DNA that matched the wild-type annexin sequence except for two mutations [855 G → A (silent); 860 A → G (converts Glu-287 to Gly-287)].--

Please replace the paragraph beginning at page 101, line 1, with the following redlined paragraph:

--The sense oligonucleotide anneals within the T7 promoter region of pET-12a, just upstream from the NdeI restriction site or the 5' end of annexin V. The following are the anti-sense and sense oligonucleotide sequence, respectively:

(Nx168 Cys TO Ala antisense)

5' GTACCTGGATCCTTAGTCATCTTCTCCGCGAGCAGCAGAAGAGCTTTCTT 3' (SEQ ID NO:4);

and (T7 sense)

5' CGAAATTAATACGACTCACTATAGGG 3' (SEQ ID NO:5).--

Please replace the paragraph beginning at page 103, line 12, with the following redlined paragraph:

--Preparation of N-Terminally Extended Annexin V (Annexin V-N-6, also referred to as modified annexin). First, a mutant annexin V cDNA (pANXVC-S) was designed in which the Cys<sub>316</sub> codon was replaced by a Ser codon, an *NdeI* site was introduced prior to the initiator Met codon, and a *BamHI* site was introduced after the stop codon. This was constructed by PCR using an annexin V cDNA (pPAP-I-1.6; Funakoshi *et al.*, 1987 Biochemistry 26:5572-5578, Cookson *et al.*, 1994 Genomics 20:463-467) as a template and two oligonucleotides, 5'-g·gaa·ttc·cat·atg·gca·cag·gtt·ctc·aga·ggc·act·gtg-3' (SEQ ID NO:6) and 5'-cgc·gga·tcc·tta·gtc·atc·ttc·tcc·gga·gag·cag-3' (SEQ ID NO:7). This DNA was ligated into the

*NdeI* and *BamHI* cloning sites in the pET12a plasmid (Novagen, Madison, WI). An oligonucleotide (5'-t-atg-gca-tgt-gac-cat-tc-3') (SEQ ID NO:8) and its inverse complement (5'-t-aga-atg-gtc-aca-tgc-ca-3') (SEQ ID NO:9) were prepared to encode six amino acid residues (Met-Ala-Cys-Asp-His-Ser) (SEQ ID NO:10) with *NdeI*-compatible overhangs at both ends. The two complementary oligonucleotides were annealed and the product was ligated into pANXVC-S that was digested with *NdeI* to produce plasmid pANXVC-S-N6. DNA sequencing of this plasmid confirmed that the intended mutations had been correctly introduced.--

Please replace the paragraph beginning at page 158, line 7, with the following redlined paragraph:

--A dimer of two modified annexin V molecules can be prepared by recombinant-DNA methods following the methods described by Tait et al., J. Biol. Chem., 270: 21594-21599, 1995, for construction and expression of chimeric molecules containing annexin V. First, PCR is performed on the annexin V cDNA template pPAP-I-1.6 with oligonucleotide primers that introduce an *NdeI* site at the 5' end and a *BamHI* site at the 3' end of the annexin V coding sequence (amino acids 1-320 + stop codon), and this PCR product is cloned by standard procedures into the *NdeI* and *BamHI* sites of plasmid pET-12a (Novagen Corp., Madison, WI) to create plasmid pET-12a-Ax1. PCR is then performed again on the annexin V cDNA template pPAP-I-1.6 with oligonucleotide primers that introduce an *NdeI* site at the 5' end and a sequence encoding the amino acids Gly-Gly-Gly-Gly-Gly-Gly (SEQ ID NO:11) followed by an *NdeI* site at the 3' end of the annexin V coding sequence (amino acids 1-320). This PCR product is then cloned by standard procedures into the *NdeI* site of plasmid pET-12a-Ax1 to create plasmid pET-12a-Ax2. Production of the dimeric annexin V molecule by cytoplasmic expression in *E. coli* from plasmid pET-12a-Ax2 is then performed by standard procedures, for example as shown by Tait et al., J. Biol. Chem., 270: 21594-21599, 1995.--